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U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM)
Quality Assurance Team

STANDING OPERATING PROCEDURE
FOR
Quality Systems GLP Critical Phases Audits (CPA)

Preparer	Date: 12/20/2000
Supervisor Approval	Date: 12/20/2000

Annual Review

Preparer	Date Due: 12/20/2001	Date Comp.
Supervisor	Date Due: 12/20/2001	Date Comp.
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CONTENTS

I. PURPOSE: This standing operating procedure (SOP) describes the responsibilities of the Quality Assurance Office with respect to GLP compliance of Directorate of Toxicology Operations (DTOX) nonclinical studies as well as all Directorate of Laboratory Sciences (DLS) analytical support and contract laboratories.

II. APPLICABILITY: It is the policy of the USACHPPM that every effort is made to assure that all studies undertaken by the DTOX and the reports of such studies are of the highest possible quality and adhere to the best standards of professional scientific endeavor. It is the further the policy of USACHPPM that the regulations of the Food and Drug Administration (FDA) (21 CFR Part 58), the Environmental Protection Agency's (EPA) (40 CFR Part 160) and the Environmental Protection Agency's (EPA) (40 CFR Part 792) for Good Laboratory Practices (GLP) in Nonclinical Laboratories be followed for all DTOX nonclinical toxicological studies. To assist in implementation of this policy, a Quality Assurance Team (QAT) has been established within the Strategic Initiatives Office (SIO), as an integral and permanent organizational unit of the USACHPPM.

III. DEFINITIONS:

A Acute nonclinical study - Nonclinical toxicology studies of two weeks or less in duration.

B Subchronic nonclinical study – Nonclinical toxicology studies of 90 days or less but more than two weeks.

C Long term nonclinical study – Nonclinical toxicology studies of longer than 90 days.

D Critical phases of nonclinical toxicology studies – The critical processes of a nonclinical study that must be periodically inspected by the laboratory's quality assurance function in accordance with GLPs. The following list identifies these critical phases, but is not necessarily all inclusive:

1. Protocol Review;
2. DTOX SOP Review;
3. DTOX Personnel Training Records;
4. Test System;
    a. Section 1 - Facilities,
    b. Section 2 - Receipt,
    c. Section 3 - Identification,
    d. Section 4 - Husbandry,
    e. Section 5 - Observations,
    f. Section 6 - Food and Water Supply.
5. Test Article;
    a. Section 1 – Facilities,
    b. Section 2 – Control,
    c. Section 3 – Receipt,
    d. Section 4 - Preparation and Analysis,
    e. Section 5 - Handling,
    f. Section 6 – Administration, Dosing and Animal Weighing.
6. Clinical Testing (clinical chemistry and hematology);
7. Necropsy;
    a. Section 1 - General Requirements,
    b. Section 2 - Necropsy Procedures,
    c. Section 3 - Solutions and Reagents,
    d. Section 4 - Tissues, Blocks and Slides,
    e. Section 5 – Necropsy Records.
9. Maintenance and Calibration of Equipment;
10. Reagents and Solutions;
11. Compliance with DTOX SOPs;
12. Compliance with DTOX protocols;
13. Final Study Report Review;
14. Study Data Review;
15. Records Storage and Archiving;
16. Specimen Storage;
17. Contract Laboratory Monitoring;

18. Analytical Chemistry Support.

IV. QUALITY CONTROL:

A Document Control – Critical phase checklists (Appendices A-Q) will be maintained in accordance with QAT SOP #1.X.

B Report Review – All critical phase inspection reports will be reviewed by the QAT team leader and the Chief, SIO, prior to delivery to DTOX management. Specifics on reporting to management are identified in QAT SOP # 3.X.

V. PROCEDURES: Toxicology studies vary in duration. They can be acute, subchronic or long-term. The following procedures identify how the QAT will conduct QAT GLP CPA.

A Checklists for all critical phases are located in the QAT SOP notebook. These checklists are used as a guide for conducting critical phase inspections.

B **Acute Nonclinical Studies:** QAT personnel will inspect ***all*** critical phases that ***occur*** during all acute nonclinical studies. Some critical phases of the acute nonclinical studies may not be inspected due to unforeseen circumstances such as:

- Phases are being completed at contract labs and cannot be audited
- QAT personnel are predisposed due to illness, vacation, or other duties that proclude these inspections.

If ***occurring*** phases are not inspected be QAT, personnel for the reasons above or other unforeseen reasons, that fact will be stated in the corresponding study QA statement to include the reason for the failure to inspect. It is the responsibility of the study director to notify the QAT when the study is to begin including the day and approximate time the critical phase is to be performed. Once notification is received, it then becomes QAT's responsibility to inspect the critical phase, document the findings and report all findings to management. The checklists contained in the QAT List of Official Forms identify the specific requirements of critical phases and are used by the QAT inspectors to conduct inspections. Serious deficiencies noted during a critical phase inspection will be brought to the immediate attention of the study director and management. The study director will promptly resolve all discrepancies before proceeding with study procedures. A written inspection report, in accordance with QAT SOP # QAT 3.X "Reporting to Management", will be issued to the study director through management (usually within three working days of the inspection). The study director will respond in writing through management by the suspense date noted on the QAT report. The written response from the study director and all documentation relative to the inspection are retained in the QAT study file. The QAT may choose to re-inspect any critical phase of the acute study where

deficiencies have been identified.

C **Subchronic Nonclinical Studies:** At least four critical phases of a nonclinical subchronic study will be inspected by the QAT over the course of the study. In addition, study data for subchronic studies should be inspected at the studies midpoint to verify the adequacy of documentation procedures. It is the responsibility of the study director to notify the QAT when the study is to begin including the day and approximate time the critical phase is to be performed. Once notification is received, it then becomes QAT's responsibility to inspect the critical phase, document the findings and report all findings to management. The checklists contained in the QAT List of Official Forms identify the specific requirements of critical phases and are used by the QAT inspectors to conduct inspections. Serious deficiencies noted during a critical phase inspection will be brought to the immediate attention of the study director and management. The study director will promptly resolve all discrepancies before proceeding with study procedures. A written inspection report, in accordance with QAT SOP # QAT 3.X "Reporting to Management", will be issued to the study director through management (usually within three working days of the inspection). The study director will respond in writing through management by the suspense date noted on the QAT report. The written response from the study director and all documentation relative to the inspection are retained in the QAT study file. The QAT may choose to re-inspect any critical phase of the acute study where deficiencies have been identified.

D **Long Term Nonclinical Study:** At least four critical phases of a Long Term Nonclinical study will be inspected by the QAT over the course of the study In addition, long-term studies data should be reviewed at 3-month intervals during the course of the study to verify the adequacy of documentation procedures. It is the responsibility of the study director to notify the QAT when the study is to begin including the day and approximate time the critical phase is to be performed. Once notification is received, it then becomes QAT's responsibility to inspect the critical phase, document the findings and report all findings to management. The checklists contained in the QAT List of Official Forms identify the specific requirements of critical phases and are used by the QAT inspectors to conduct inspections. Serious deficiencies noted during a critical phase inspection will be brought to the immediate attention of the study director and management. The study director will promptly resolve all discrepancies before proceeding with study procedures. A written inspection report, in accordance with QAT SOP # QAT 3.X "Reporting to Management", will be issued to the study director through management (usually within three working days of the inspection). The study director will respond in writing through management by the suspense date noted on the QAT report. The written response from the study director and all documentation relative to the inspection are retained in the QAT

study file. The QAT may choose to re-inspect any critical phase of the acute study where deficiencies have been identified.

VI. SAFETY CONSIDERATIONS: Compliance with all division and branch safety procedures, SOPs and the DLS Chemical Hygiene Plan requirements is mandatory curing the conduct of all QAT inspections.

VII. REFERENCES:

A USFDA Federal Food, Drug and Cosmetic Act (FFDCA), 21 CFR 58 (1979), latest edition.

B USEPA Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 40 CFR 160 (1984), latest edition.

C USEPA Toxic Substances Control Act (TSCA), 40 CFR 792 (1983), latest edition.